

SLEEP APNEA IN GOUT PATIENTS: UNDERLYING MECHANISMS AND SHARED PATIENT SUBTYPES

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Abstract

Acute and chronic inflammation in gout causes permanent tissue damage, leads to restricted mobility and significantly reduces the quality of life. Obstructive sleep apnea (OSA) is a breath disordered sleep disease, which is a risk factor for respiratory, cardiovascular and cerebrovascular complications, nephropathy and other diseases.

The aim of this paper was to explore the underlying mechanisms and shared pathways, targets and biomarkers of sleep apnea and gout, aiming at providing clear evidence about whether OSAS patients have higher serum uric acid levels and more susceptible to gout.

Materials and methods. We conducted this literature analysis on relevant studies, which were identified via electronic databases from inception to May 30, 2020. Study selection was conducted according to predesigned criteria, and two authors independently extracted data from included studies.

Results. In the period from 2010 to 2020, 4 large-scale population-based studies were conducted to prove that OSA can affect the level of uric acid, resulting in increased incidence of gout in OSA patients. Only one big population-based study during 2010-2020 assessed the development of OSA against the background of gout. The data from these studies showed an undoubted relationship between the two diseases, but to date it is not completely known how much it is due to common risk factors and how interlinked the development mechanisms are.

Conclusions. Relationship between OSA, gout, and pro-inflammatory/metabolic disorders is therefore complex; with some recent studies indicate different mechanisms may play a role in the development of OSA-gout combination. The inconsistency in results may indicate the presence of several patient profiles or subtypes with gout-OSA comorbidity: combined with metabolic syndrome (most common), combined with renal dysfunction without obesity, and others (dietary violations, genetic diseases, acidosis).

This paper reviews the research progress on the relationship between the epidemiological characteristics of OSA and the incidence of gout, with the insight into pathogenetic mechanisms of comorbidity.

Keywords: gout, obstructive sleep apnea, gout comorbidities, gout patients' subtypes, uric acid, purine synthesis.

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1. Introduction

Gout is one of the most common rheumatic diseases in the world, which affects about 1.14 % of the general population in China [1], and from 1.4 to 2.5 in other countries [2–4]. According to different sources, the incidence of OSA in the general population is 4–10 % [5]. Clinical manifestations of gout include osteoarthritis and associated inflammation as much as system disorders linked to impaired purine metabolism. Hyperuricemia due to inefficient excretion or, in some cases, hyperproduction of purines, is often accompanied by metabolic disorders, obesity and hypertension which gradually reduce the quality of life in gout patients. OSA episode is characterized by a major upper airway collapse during sleep and subsequent decrease in blood oxygen saturation. Some studies showed that hypoxemia in OSA can affect the levels of blood uric acid, or lead to the increase in gout incidence or aggravation of symptoms in gout patients [3]. The purpose of this paper is to explore the relationship between gout and OSA, to provide new ideas for diagnostic and treatment strategies.

2. Literature review

2. 1. Population-based studies

Obstructive sleep apnea is characterized by repeated episodes of difficulty in breathing as a result of obstruction in the upper respiratory tract, which usually causes a decrease in blood oxygen saturation and fragmentation of sleep, and may be accompanied by snoring and excessive daytime sleepiness [6, 7].

According to different sources, the incidence of OSA in the general population is 4–10 % [2], while in men it is more common than in women [5]. Due to the fact that hypoxia in OSA can be one of the factors in the development of nephropathy, and, as a result, may potentially lead to decreased uric acid excretion by the kidneys, several cohort studies were conducted to identify the frequency of OSA-gout combination. Zhang et al [8] in 2014 conducted a matched cohort study on 9865 newly diagnosed sleep apnea patients and 43598 comparators, to find that patients with sleep apnea had a 20 % higher risk of developing gout (HR=1.2, 95 % CI: 1.0–1.4). The corresponding hazard ratios over 6-months, 1-year, and 2-years were 1.7 (95 % CI: 1.1–2.8), 1.6 (95 % CI: 1.2–2.1), and 1.4 (95 % CI: 1.1–1.7), respectively.

Later, in 2018 Blagojevic-Bucknall et al [3], analyzed the data of 15879 patients with OSA (in comparison with 63296 controls), and found that the frequency of gout was almost twice as high in patients with OSA. A meta-analysis by Tingting Shi et al [1], published in 2019, included 18 independent studies and 157 607 patients (32395 with OSA, 125212 without OSA, of which 12 262 with gout). Deep statistical analysis of the data showed a connection between the development of OSA and an increase in the level of uric acid in blood serum (WMD=52.25, 95 % CI 36.16–64.33), while the relationship between OSA and gout was lower than in previous studies (HR =1.25, 95 % CI 0.91–1.70). A study by van Durme et al [4], published in 2020, which included 111509 patients with OSA (compared to 210241 without one), showed even more inconsistent results. In the initial analysis, the risk of gout in patients with OSA was also significantly increased (OR 1.86; 95 % CI (1.71–2.02), however, after adjusting for age, smoking, alcohol, diabetes and nephropathy, the difference between patients with OSA and the control group almost disappeared (OR 1.05; 95 % CI 0.96–1.16) (Fig. 1).

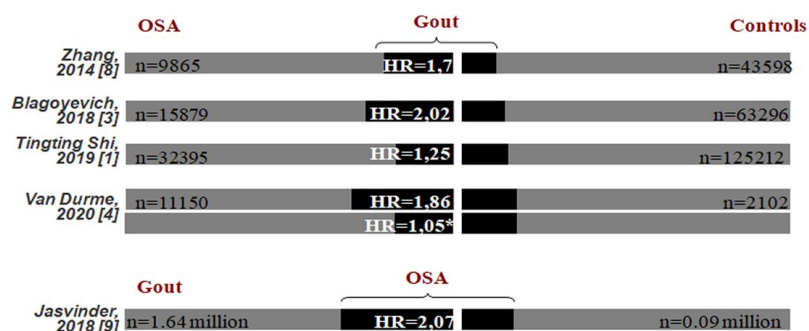


Fig. 1. Incidence of OSA-gout and gout-OSA combinations in recent large-scale population-based studies (2010-2020); *after adjusting for age, smoking, alcohol, diabetes and nephropathy

Therefore, based on data from recent population-based studies, OSA cannot be considered a full-fledged predictor of gout, but there is an undoubted connection between these diseases. Partly, it can be explained by comorbidity with diabetes, obesity and other metabolic disorders that are characteristic for both of these diseases. The pathophysiological mechanisms discussed below can also serve as a prerequisite for the development of OSA against the background of gout. To the best of our knowledge, at the time of this publication, there is only one population-based study on gout-OSA relationship analyzing data from 1.74 million participants over the age of 65 [9]. The incidence of OSA was 14.3 per 1,000 person-years in patients with gout, compared with 3.9 per 1,000 person-years without gout, with HR=2.07 (95 % CI 2.00–2.15 %), which is significantly higher than the incidence of gout in patients with OSA, even taking into account hypertension and hyperlipidemia.

2. 2. Shared mechanisms of development

Persistent hyperuricemia in gout is caused in most cases by decreased renal excretion of urates, including patients taking diuretics for a long time, as well as in patients with renal diseases, leading to a decrease in glomerular filtration rate (**Fig. 2**). Purines of food origin (beer, meat, caviar, legumes, coffee, cocoa, chocolate, strong tea) significantly affect the level of uric acid. Ethyl alcohol causes the decomposition of nucleotides in the liver and increases formation of lactic acid, which, like other organic acids, blocks the secretion of urates in the renal tubules. The exacerbation of hyperuricemia in all types of acidosis is also associated with this. Medicines, in particular nicotinic acid, thiazide and loop diuretics, ethambutol, low doses of salicylates, can also lead to an increase in uric acid content [10].

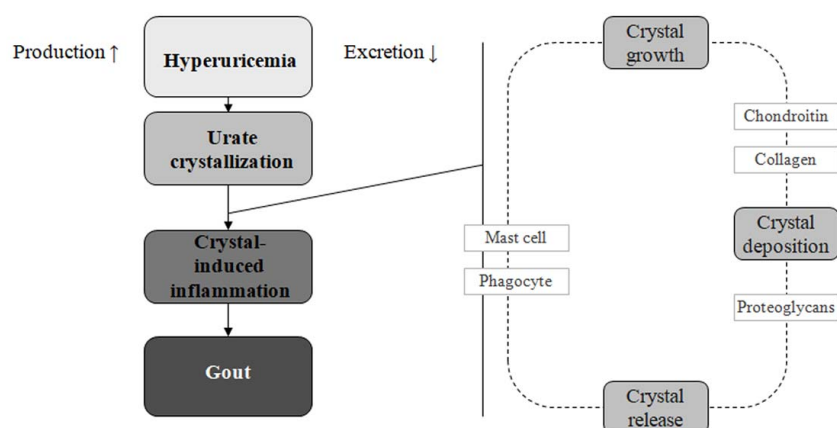


Fig. 2. Mechanisms of inflammation induced by urate crystals in the development of gout and the urate crystallization circle. Adapted from Mclean et al. 2011 [10]

Sleep quality also may be associated with impaired renal function. According to Chan Won Kim et al [14] in healthy subjects (n=241 607), a decrease in glomerular filtration rate was associated with a decrease in average sleep duration. A number of studies have traced the relationship between OSA and nephropathy associated with the development of type 2 diabetes mellitus [15], but to our best knowledge there is no published data on the development of gout in these cases.

The effect of diuretics on the development of OSA is not yet fully understood. Some researchers suggest that the use of diuretics, especially in patients with arterial hypertension, can reduce the severity of OSA [11, 12]. This may depend on a fact that sodium intake in patients with OSA is significantly higher: it was shown that above a cut off value of 2.4 g/day predicted moderate to severe OSA (area under the ROC curve of 0.78) [13]. Consequently, forbearance from diuretics in the treatment of gout may be one of the reasons for the deterioration of OSA.

According to numerous studies, obesity is an independent risk factor in the development of gout and OSA. Visceral fat is a metabolically active tissue that produces a number of pro-inflammatory and vasoactive cytokines. Against the background of metabolic syndrome (MS) multiply

changes occur which may lead to the development of gout (system inflammation, hyperinsulinemia, purine synthesis de novo) and OSA (dyslipidemia, hyperglycemia, sympathetic activation).

In numerous studies on the risk of developing MS in patients with OSA, results have been obtained that make it possible to consider OSA as an independent predictor of MS, however, due to the fact that the development of both conditions is very prolonged in time, it is difficult to get an answer which developed earlier. Conversely, metabolic syndrome and its components – in particular, obesity and insulin resistance — can be crucial in the development of sleep disorders, which is why it was proposed in other studies to consider OSA as a “metabolic disorder” itself and a component of MS [16].

2. 3. Role of inflammation in the development of OSA

Gout is associated with an increase in biochemical markers of inflammation, due to the development of an immune response to the deposition of urate crystals [17]. Moreover, the reverse development of the symptoms of gouty arthritis depends on the development of anti-inflammatory mechanisms of macrophage and synoviocytic origin. In recent years, studies have also noted an increase in one or more biochemical markers of inflammation in patients with OSA, which is an aggravating factor in the development of cardiovascular complications (**Fig. 3**). Also, some researchers believe that hypoxemia in patients with OSA can inhibit the anti-inflammation pathways and lead to slower recovery, but at the moment this issue has not yet been fully studied.

Obesity, which is a common risk factor for OSA and gout, can cause an increase in biochemical markers of inflammation due to the ability of adipose tissue to produce adipokines, including TNF- α and IL-6. However, in their study, Steiropoulos et al [18] compared two groups of patients with obesity, and showed that under the same conditions of weight and degree of obesity, the risk of developing OSA is much higher in patients with elevated TNF- α .

The combination of gout with impaired glucose metabolism is found according to various sources in 7–74 % of cases [19, 23]. Such a wide range is determined by various used criteria: from impaired glucose tolerance to the clinical manifestations of diabetes. At the same time, among patients with DM type 2, hyperuricemia occurs in almost half of cases [20], however, cases of gouty arthritis are rare (0.1–9 %) [21–23]. This is explained by the fact that with poor metabolic control of glucose, the level of uric acid in the blood is low due to the uricosuric effect of glucose in high concentrations [19]. It was also shown that insulin is a direct opponent of glucose in uric acid homeostasis, and with hyperinsulinemia, urate excretion decreases and its reabsorption in the kidneys increases [24].

Changes in glucose metabolism are also noted along with the development of OSA. As numerous studies show, there is a strong connection between diabetes and OSA, and many of obese patients have both.

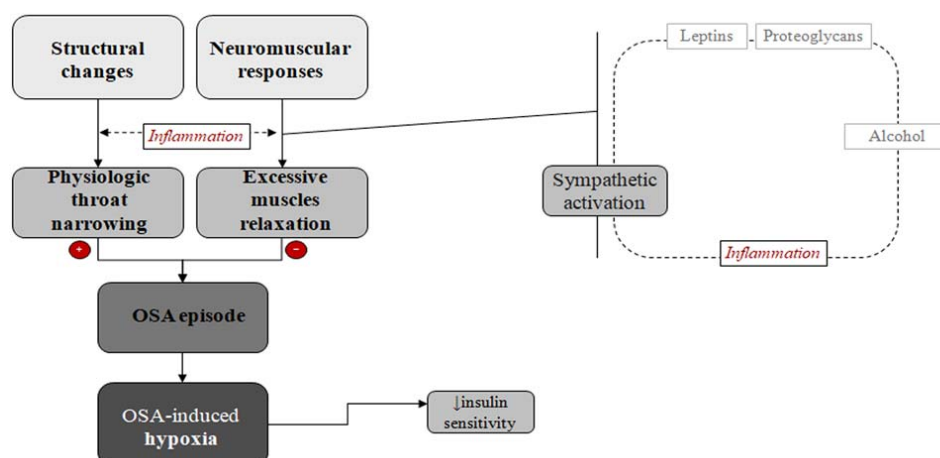


Fig. 3. Mechanisms of inflammation involved in the development of OSA and its complications.
Adapted from Montesi et al. 2016 [26]

An inflammatory reaction due to hyperuricemia and urates deposition can cause oxidative stress. However, some other studies show that uric acid also has anti-oxidant properties. According to a comparative study of oxidative stress markers [25] in 30 patients with gout, only Malondialdehyde was increased. Thus, in patients with gout during the period of exacerbation, lipid destruction can occur under the influence of oxidative stress, which, in turn, can affect the development of the metabolic syndrome.

Oxidative stress plays a key role in the pathogenesis of OSA. Respiratory tract obstruction and hypoxemia lead to the activation of oxidative stress markers cascade, which in turn may be responsible for the development of metabolic and cardiovascular changes in OSA [27]. This pathway is primary for OSA, but its activation in patients with gout can lead to a deterioration in sleep patterns and significantly worsen the course of OSA.

3. Discussion. Patients subtypes

In most of the studies mentioned above, the relationship between OSA, gout, and pro-inflammatory/metabolic disorders varied significantly depending on the number of patients in the sample with smaller studies reported the lack of a statistically significant relationship. This may indicate, among other things, that there are several patient profiles or subtypes with a gout-OSA combination.

The most common cases include a combination of OSA, gout, and metabolic syndrome (Fig. 4, A). In this case, against the background of obesity and insulin resistance, there is a violation of purine excretion, due to the ability of insulin to slow the clearance of uric acid in the proximal tubules of the kidneys. At the same time, hyperactivation of the sympathetic system and dysregulation of the hypothalamic-pituitary axis, characteristic for the development of MS, lead to sleep disturbances. Subsequently, hypoxia during OSA stimulates excessive purine synthesis by adipose tissue, and fructose-urate metabolic pathway triggers major inhibitors of AMP-activated protein kinase, which can aggravate the course of MS, forming a vicious cycle.

The combination of gout and OSA without obesity is much less common and is accompanied, first of all, by renal dysfunction (Fig. 4, B). In this case, a violation of the urates secretion leads to gout, meanwhile hypertension and the activation of the inflammatory cascade lead to the subsequent development of OSA.

The presence of other profiles of patients with gout and OSA, which are even less common, cannot be ruled out (Fig. 4, C). Hereby, urine acid level is significantly influenced by purines of food origin, and ethyl alcohol causes the decay of nucleotides in the liver and blocks the secretion of urates in the renal tubules. Patients with gout against the background of prolonged alcoholism and nutritional disorders can observe episodes of OSA associated with the destruction of the nervous system pathways. Some genetic diseases can also affect both the synthesis of purines de novo and the development of sleep disorders. And finally, systemic acidosis of various origins leads to exacerbation of hyperuricemia, synthesis of reactive oxygen species, oxidative stress and neurohumoral changes.

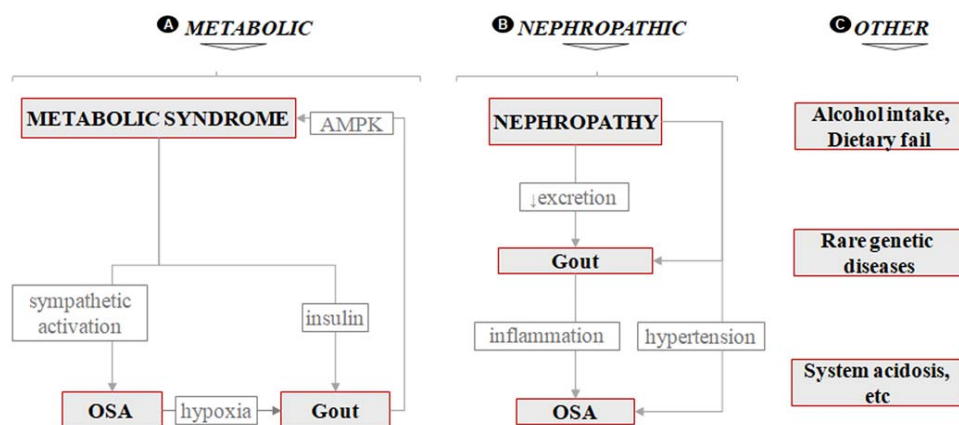


Fig. 4. Major subtypes of goat-OSA combination, according to different pathways involved; AMPK – 5' adenosine monophosphate-activated protein kinase

Study limitations. First, our review was not systematic and only took into account recent papers, thus the results do not fully describe all the details of relationship between OSA and gout. Second, the described codependency was greatly limited by the sample size. Third, most authors mentioned in review did not directly observe OSA-gout patients, only working with data from clinical databases. It is therefore possible that other unmeasured factors might have affected the relationship between OSA and gout. Finally, the combination of OSA, gout and metabolic syndrome greatly depends on gender, with gout more often present in men and metabolic syndrome in women. Stratification based on gender therefore is both necessary and greatly complicates results interpretation.

Prospects for further research. One of the ways to determine the nature of relationship between gout and sleep apnea would be through a large scale study conducted on patients of one hospital with stratification of patients according to OSA-gout subtypes. It would allow to explain the inconsistency in currently published data and include the possibility that the presence of OSA may serve as an indicator of gout severity.

4. Conclusion

All recently published studies confirm connection between the development of OSA and an increase in the level of uric acid in blood serum. However, only one big population-based study during 2010–2020 assessed the development of OSA against the background of gout. According to this study, incidence of OSA was 14.3 per 1,000 person-years in patients with gout, compared with 3.9 per 1,000 person-years without gout, with HR=2.07 (95 % CI 2.00–2.15 %), which is significantly higher than the incidence of gout in patients with OSA, even taking into account hypertension and hyperlipidemia.

The inconsistency in results obtained in previous studies may indicate the presence of several patient profiles or subtypes with gout-OSA comorbidity: combined with metabolic syndrome (most common), combined with renal dysfunction without obesity, and others (dietary violations, genetic diseases, acidosis).

It is therefore important to note that in addition to gout, there are a large number of diseases that can be accompanied by sleep disorders and a variety of related symptoms, including daytime sleepiness. An isolated assessment of the external manifestations of OSA during a direct interview with a patient with gout cannot be the basis for a final diagnosis. Despite the fact that in typical cases it is possible with a fairly high probability to suspect the gout-OSA on the basis of the available symptoms and signs, at the moment there is no reliable way to diagnose OSA with purely clinical approach, and the diagnosis must be confirmed by instrumental methods of research. In this regard, the development of special questionnaires for the primary detection of OSA in patients with gout is one of the priority areas of research.

Conflict of interest statement

The authors declare that they have no conflicts of interest.

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